STATUS OF CLAIMS

Claims 1-41 are pending in the application. Claims 23-39 were previously withdrawn from consideration pursuant to a restriction requirement. Thus, Claims 1-22 and 40-41 are currently under examination.

REMARKS

Rejection Under 35 USC § 103(a) Over STAMLER and SOGO

Claims 1-22, 40 -41 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Stamler et al, U.S. Patent No. 6,087,479 (STAMLER) in combination with the article, Sogo et al, "S-Nitrosothiols cause prolonged, nitric oxide mediated relaxation in human saphenous vein and internal mammary artery: therapeutic potential in bypass surgery" (SOGO). This rejection is respectfully traversed.

For a proper obviousness rejection under 35 U.S.C. 103, the differences between the subject matter sought to be patented and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. §103. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. MPEP 2141. " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), quoting *In re Kahn* , 441 F.3d 977, 988, (Fed. Cir. 2006). It should be noted that the prior art reference (or references when combined) must teach or suggest all the claimed features. "When determining whether a claim is obvious, an examiner must make 'a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art.' ... Thus, 'obviousness requires a suggestion of all limitations in a claim.' ..." *Ex parte Wada and Murphy*, BPAI Appeal No. 2007-3733, January 14, 2008 (emphasis in original) (citations omitted). In addition, there must be a reasonable expectation of success. See MPEP 2143.02.

Moreover, rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006), *cited with approval in, KSR Int'l v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740-41, 82 USPQ 1385, 1396 (2007). As explained below, none of the references alone or in combination provides any reason or suggestion to combine the references to arrive at the present invention. *In re Nilssen*, 851 F2d. 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988).

Claim 1 provides for a medical article comprising a first polymer matrix having a first nitric oxide donor compound disposed within the first polymer matrix and a second polymer matrix having a second nitric oxide donor compound disposed within the second polymer matrix. The second nitric oxide donor compound differs from the first nitric oxide donor compound, and the first polymer matrix is chemically distinct from the second polymer matrix. The medical article is adapted, after placement at a delivery position on or within the body of a patient, for local delivery of the first nitric oxide donor compound and a nitric oxide product of the first nitric oxide donor compound and for local delivery of the second nitric oxide donor compound and a nitric oxide product of the second nitric oxide donor compound.

In contrast to the present invention, STAMLER provides:

> [a] method for preventing adverse effects associated with the use of a medical device in a patient by introducing into the patient a device of which at least a portion includes a prophylactic or therapeutic amount of a nitric oxide adduct. The nitric oxide adduct can be present in a matrix coating on a surface of the medical device; can be coated per se on a surface of the medical device; can be directly or indirectly bound to reactive sites on a surface of the medical device; or at least a portion of the medical device can be formed of a material, such as a polymer, which includes the nitric oxide adduct. Also disclosed is a method for preventing adverse effects associated with the use of a medical device in a patient by introducing the device during a medical procedure and before or during said procedure locally administering a nitric oxide adduct to the site of contact of said device with any internal tissue.

(Abstract, emphasis added).

The Examiner agrees that STAMLER does not explicitly teach "including two different nitric oxide donors in the same device" (emphasis added) but notes that STAMLER includes

"two nitric oxide donors in [a] single device in different portions, e.g. device itself and its coating." (Office Action, page 4, emphasis added). With regard to the later quotation, it is to be kept in mind that the "two nitric oxide donors" are the same and are *not* different from one another. The Examiner also takes the position that STAMLER discloses "that the material of the medical device [is] different from the coating matrix." (Office Action, page 3).

Thus, in the final analysis, STAMLER does not teach or suggest a medical article comprising *a first polymer matrix having a first nitric oxide donor compound disposed within the first polymer matrix; a second polymer matrix having a second nitric oxide donor compound disposed within the second polymer matrix, said second nitric oxide donor compound differing from said first nitric oxide donor compound;* nor does STAMLER teach or suggest a medical article *adapted, after placement at a delivery position on or within the body of a patient, for local delivery of said first nitric oxide donor compound and a nitric oxide product of said first nitric oxide donor compound and for local delivery of said second nitric oxide donor compound and a nitric oxide product of said second nitric oxide donor compound* since these nitric oxide donors have been described as being chemically different.

It is also maintained by the Applicant that STAMLER's listing of alternative strategies is not sufficient to support the Examiner's interpretation of STAMLER as describing the simultaneous inclusion of a nitric oxide donor in the device itself and in a coating on the device. For example, in the Abstract, STAMLER states (emphasis added) (noting use of the singular term "adduct"):

> The nitric oxide adduct can be present in a matrix coating on a surface of the medical device; can be coated per se on a surface of the medical device; can be directly or indirectly bound to reactive sites on a surface of the medical device; ***or*** at least a portion of the medical device can be formed of a material, such as a polymer, which includes the nitric oxide adduct.

STAMLER further states at col. 9, lines 48-64 (emphasis added):

> As mentioned above, the medical device or instrument may be made, such that at least in those portions of it which come into contact with blood, blood components or products, or vascular tissue, include a nitric oxide adduct. The nitric oxide adduct can directly or

> indirectly be linked to a synthetic material from which all or a portion of the device is formed....
>
> In another embodiment mentioned above, the nitric oxide adduct can be incorporated into a natural or synthetic matrix which is then used to coat those same contact surfaces of the device [i.e., those portions of the device which come into contact with blood, blood components or products, or vascular tissue]. The matrix can be a liquid into which the nitric oxide adduct has been mixed, which is then coated onto the contact surfaces of the medical device or instrument and then allowed to "set", dry, polymerize or otherwise become solid or semisolid....

Nowhere in STAMLER is it taught or suggested to employ first and second chemically distinct polymer matrices, *each having a nitric oxide donor disposed therein*. It is also again noted that the Examiner has agreed that the STAMLER does not teach including two different nitric oxide donors in the same device.

The Examiner then turns to SOGO stating that SOGO teaches the "administration of two different nitric oxide donors simultaneously" (Office Action, page 4). It is respectfully submitted that the Examiner has misinterpreted SOGO.

SOGO describes a study of the performance of certain S-nitrosothiols in causing prolonged, nitric oxide-mediated relaxation in human saphenous vein and internal mammary artery for by-pass surgery. SOGO also describes the preparation of test tissue (in the form of rings of tissue) and the suspension of the tissue samples in an organ bath. (See page 1237, col.2). In the experimental protocol section of SOGO it is recited that four NO donor drugs were selected for testing: (1) N-(S-nitroso-N-acetylpenicillamine)-2-amino-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (RIG200), (2) S-nitrosoglutathione (GSNO), (3) glyceryl trinitrate (GTN) and (4) sodium nitroprusside (SNP) (see page 1237), two of which are S-nitrosothiols.

It is important to note that SOGO does not describe the administration of two different nitric oxide donors simultaneously. More particularly, in the experimental protocol section SOGO states that "[e]ach ring was randomly allocated to treatment with increasing concentrations . . . of either RIG200, GSNO, SNP or GTN in organ baths, and was treated with each concentration of drug until the relaxation reached plateau . . ." (see page 1237) (emphasis added). Thus, the testing in SOGO was done by using one drug serially in various concentrations.

Nowhere in SOGO is described any combination of NO donor compounds. Rather SOGO presents the drugs, for example, nitrosoglutathione and N-(S-nitroso-N-acetylpenicillamine) as alternatives, rather than as a combination.[1] There is no description of two or more different drugs being tested on the same tissue simultaneously.

The Examiner's statement that SOGO "recognized and suggested administration of two different nitric oxide donors simultaneously to improve more than one function in coronary patients" (Office Action, page 8) is simply not supported as noted above in the text cited from SOGO. In this regard, the Examiner has argued as follows:

> Sogo et al. teach that S-nitroso-N-acetyl-D,L-penicillamine and S-nitrosoglutathione produce more relaxation of vessel walls than commonly used NO donors, and more specifically, teach that the relaxation caused by S-nitroso-N-acetyl-D,L-penicillamine was more sustained, and S-nitrosoglutathione selectively dilates human arteries in vitro and in vivo, and their use might improve the outcome of coronary artery bypass (page 1237, left col.; page 1241, right col.; page 1243, left col.).

However, the preceding hardly suggests the administration of two different nitric oxide donors simultaneously.

Moreover, the testing in SOGO was not done with the drugs being in a polymer matrix and SOGO does not teach or suggest that two different drugs may be used in the same device.

The Examiner states that at the time of the invention, STAMLER "recognized providing NO adduct in a coating of a device, and also recognized providing NO adduct in the material forming the device, and recognized administering nitric oxide adduct in combination with active agent that can be linked to the surface of the device . . .[and which] could be two NO adducts from one device." (Office Action, page 6).

This interpretation is in conflict with the Examiner's admission that STAMLER does not teach two different NO adducts. While STAMLER teaches that the nitric oxide adduct can be applied in combination other therapeutic agents such as anti-thrombogenic agents, STAMLER does not teach or suggest administering two different nitric oxide adducts from the same device

[1] In addition to the preceding evidence, see further the experimental results in Sogo et al., in which response curves for RIG200 (N-(S-nitroso-N-acetylpenicillamine) are *separate and distinct* from response curves for GSNO (nitrosoglutathione) and there are no data or textual support for a combination of two or more NO donor compounds. (*See* Figures 3, 4, 5, 6, and their accompanying text.)

as claimed. (Nor does STAMLER teach or suggest administering the nitric oxide adduct and the second therapeutic agent from chemically distinct polymeric matrixes as claimed; instead, as noted in the Office Action at page 6, the "second therapeutic agent that has anti-thrombogenic effect is provided along with NO adduct in the coating [i.e., in the same matrix] or linked to the reactive sites in or on the body of the device [i.e., not in a matrix at all].")

This interpretation is also in conflict with SOGO which describes the possible use of a single agent such as an S-nitrosothiol to provide both a vasospasm and perhaps an anti-thrombus benefit. (See page 1243, col. 2).

SOGO as the secondary reference thus does not remedy the deficiencies in STAMLER. Specifically, SOGO does not teach or suggest first and second chemically distinct polymer matrices, each having a nitric oxide donor disposed therein. Nor does SOGO teach or suggest administration of two different nitric oxide donors to the same tissue.

Any combination of STAMLER and SOGO is merely based on the use of undue hindsight, which is prohibited. *See Akso N.V. v. U.S. International Trade Commission*, 808 F.2d 1241, 1480-81, 1 U.S.P.Q.2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied,* 482 U.S. 909 (1987), *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 874, 228 U.S.P.Q. 90-99 (Fed. Cir. 1985). Also see MPEP § 2142, second paragraph. The combination is based upon *applicant's own disclosure*, rather than the teachings within the four corners of SOGO and STAMLER.

The courts have been clear that there must be some *articulated reasoning with some rational underpinning* to support the legal conclusion of obviousness. *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006), *cited with approval in, KSR Int'l v. Teleflex, Inc.*, 127 S. Ct. 1727, 1740-41, 82 USPQ 1385, 1396 (2007). Applicants state that the Examiner has not provided a rational underpinning to support the combination of two different NO donor compounds in two different matrices.

In light of the above remarks, reconsideration and withdrawal of this rejection of the claims under 35 U.S.C. § 103 is respectfully requested.

CONCLUSION

Applicants submit Claims 1-22 and 40-41 are in condition for allowance. Reconsideration is requested and an early notice of allowance is earnestly solicited. It is believed that this Amendment and Response is being submitted in time for an Advisory Action should the Examiner require further changes to the Claims. Should the Examiner be of the view that an interview would expedite consideration of this Response or of the application at large, the Examiner is requested to telephone the Applicant's attorney at the number listed below in order to resolve any outstanding issues in this case.

Dated: January 14, 2010

Respectfully submitted,

/ Rosemary M. Miano/
Rosemary M. Miano
Registration No. 29,674

Attorney for Applicant
Mayer & Williams PC
251 North Avenue West, 2nd Floor
Westfield, NJ 07090
(908) 518-7700 Tel.
(908) 518-7795 Fax